**2003-821289/77** B03 **ONOY 2002.03.01**
ONO PHARM CO LTD *JP 2003252794-A
2002.03.01 2002-056224(+2002JP-056224) *(2003.09.10)* A61K 45/00, 31/426, A61P 1/00, 1/16, 3/10, 7/00, 7/06, 11/00, 11/06, 13/12, 15/00, 19/02, 21/00, 25/00, 25/28, 27/12, 29/00, 31/12, 31/18, 35/02, 37/02, 43/00, C07D 277/36

**Agent for controlling apoptosis containing aldose reductase inhibitor, useful for dementia, arthritis, HIV, AIDS, autoimmune disorders, liver disease, nephritis**

**C2003-231406**

B(7-F1, 14-A1B1, 14-C9, 14-E10, 14-F3, 14-F4, 14-F8, 14-G2D, 14-H1, 14-J1A4, 14-J5, 14-K1A, 14-N3, 14-N10, 14-N12, 14-N17, 14-S1, 14-S4) .11

NOVELTY

An agent for treating or preventing a disease associated with apoptosis contains an aldose-reductase inhibitor as the active component.

ACTIVITY

CNS-Gen.; Anti-HIV; Cytostatic; Antiarthritic; Ophthalmological; Dermatological; Antiulcer; Antithrombolytic; Antianemic; Muscular-active; Antidiabetic; Hepatotropic; Respiratory-Gen.; Nephrotropic.

MECHANISM OF ACTION

None given.

USE

The agent is used to treat dementias, such as Alzheimer type senile-dementia, cerebrovascular damage, neurodegeneration; HIV, HTLV related disease such as AIDS, AIDS-related disease, adult T-cell leukemia, hair like-cell leukemia, the myelosis, a respiratory-organ failure, arthritis, uveitis; systemic lupus erythematosus, collagen disease such as a rheumatoid arthritis; autoimmune disease such as ulcerative colitis, Sjogren's syndrome, primary biliary cirrhosis, spontaneous thrombocytopenia purpura, autoimmune hemolytic anemia, myasthenia gravis, insulin-dependent (type I) diabetes, myelodysplastic syndrome, thrombocytopenia, periodic thrombocytopenia, aplastic anemia, spontaneous thrombocytopenia, disseminated intravascular coagulation, hepatic disorders, such as hepatitis virus C, A, B, or F type, iatrogenic hepatitis, liver cirrhosis, adult respiratory distress syndrome, prostate hypertrophy, uterine myoma, bronchial asthma, various congenital malformation disease,



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nephritis, senile cataract, chronic fatigue syndrome, and muscular dystrophy (claimed). The agent can be used with another agent.

ADVANTAGE

IMR-32 cells were cultured in serum-free medium for 9 hours, in the presence or absence of 30 micro M (E,E)-5-(2-methyl-3-phenyl-2-propenylidene)-4-oxo-2-thioxo-3-thiazolidine acetic acid. Apoptosis was detected with TUNEL dye. Optical density was about 1.45 for the culture without the agent, and about 1.35 when the agent was present.

SPECIFIC MATERIALS

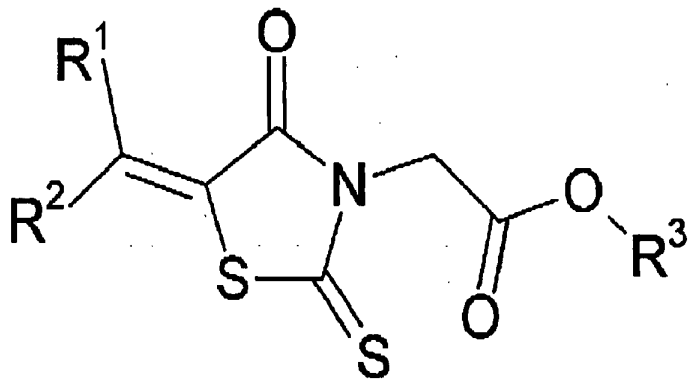
The aldose-reductase inhibitor is (E,E)-5-(2-methyl-3-phenyl-2-propenylidene)-4-oxo-2-thioxo-3-thiazolidine acetic acid.

ADMINISTRATION

1-1000 mg/day orally or 1-100 mg/day parenterally for an adult

TECHNOLOGY FOCUS

Organic Chemistry - Preferred Inhibitor: The inhibitor is a rhodanine derivative of formula (I), or its salts.




(I)

$R^1$, $R^2$ = Ar, H, 4-7C cycloalkenyl or 4-7C cycloalkyl (optionally substituted by one or more 1-4C alkyl), anthryl, naphthyl, Ar', Het', styryl, 2-(1-4C alkyl)-styryl or phenylethynyl;

$R^1$+$R^2$ = tetramethylene or pentamethylene;

$R^3$ = H, 1-12C alkyl, 7-13C aralkyl, 4-7C cycloalkenyl or 4-7C cycloalkyl (optionally substituted by one or more 1-4C alkyl) or Ar;

Ar = phenyl {optionally substituted by halo, trifluoromethyl, hydroxy, nitro, carboxyl, amino (optionally substituted by 1-4C alkyl), 1-4C alkyl (optionally substituted by hydroxy, phenyl, Het), 1-4C

alkoxy, 1-4C alkylthio, phenyl, Het}; or
Het = heterocyclyl containing N, O and/or S (optionally substituted by halo, trifluoromethyl, phenyl, nitro, hydroxy, carboxyl, amino optionally substituted by 1-4C alkyl, 1-4C alkyl, 1-4C alkoxy, 1-4C alkylthio);
Het' = as for Het, where the substituent may also be oxo;
Ar' = as for Ar, where the substituent on Het may also be oxo.
(11pp2603DwgNo.0/5)